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Clinical importance of hyperhomocysteinemia in patients with ischemic stroke**

Znaczenie kliniczne hyperhomocysteinemii u chorych z udarem niedokrwiennym mózgu

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S u m m a r y

Introduction. Homocysteine is an amino acid, produced during the metabolism of methionin to cystein. A high concentration of total homocysteine is a strong and independent risk factor for cardiovascular diseases.

Aim. The aim of the study was to analyze the homocysteine concentrations in the blood of patients in the early stage of stroke according to clinical assessment in the Oxfordshire Community Stroke Project (OCSP) classification.

Material and methods. We examined the sera of 193 patients in the early stage of stroke. Total plasma homocysteine concentrations were measured by fluorescence polarisation immunoassay (FPIA-ABBOTT).

Results. We did not find statistical difference of concentration of homocysteine between control group vs group of stroke patients. We found an increased pathological homocysteine concentration in 35.3% subjects and compared to the total number group of examined stroke patients this concentration was significantly higher in the (lacunar circulation infarct) LACI group ($P < 0.007$). A homocysteine concentration > 15 μmol/l was observed in 41.9% of LACI patients. This was the highest statistically significant concentration ($P < 0.02$) compared to the other groups of patients.

Conclusions. Our results determined the association of lacunar stroke with an increased homocysteine concentration as independent risk factor.

Key words: homcysteine, ischemic stroke, LACI

S t r e s z c z e n i e

Wstęp. Homocysteina jest aminokwasem powstającym w czasie metabolizmu metioniny do cysteiny. Podwyższony poziom homocysteiny jest niezależnym czynnikiem ryzyka dla chorób układu sercowo-naczyniowego.

Cel pracy. Celem tego badania była analiza poziomu homocysteiny w surowicy krwi pacjentów we wczesnym okresie niedokrwiennego udaru mózgu. Do klasyfikacji chorych użyto skale Oxfordshire Community Stroke Project (OCSP)

Materiał i metody. Przebadano surowicę uzyskaną od 193 chorych w ostrym okresie niedokrwiennego udaru mózgu. Całkowity poziom homocysteiny oznaczono przy pomocy immunofluorescencyjnej polaryzacji (FPIA-ABBOTT).

Wyniki. Nie stwierdzono statystycznej różnicy poziomu homocysteiny u chorych z udarem vs grupa kontrolna. Podwyższony poziom homocysteiny stwierdzono u 35,3% chorych i w porównaniu z całą grupą chorych z udarem był on najwyższy w grupie z udarem lakunarnym (LACI) ($p < 0,007$). Poziom homocysteiny powyżej 15 μmol/l stwierdzano u 41,9% chorych z LACI. To był najwyższy, statystycznie znamienny ($p < 0,02$), poziom w porównaniu z innymi badanymi grupami chorych z udarem.

Wnioski. Wyniki wskazują na istotną rolę homocysteiny jako niezależnego czynnika ryzyka dla niedokrwiennego udaru mózgu typu LACI. Nie stwierdzono natomiast, aby poziom homocysteiny był niezależnym czynnikiem ryzyka dla wystąpienia udaru niedokrwiennego mózgu.

Słowa kluczowe: homocysteina, udar niedokrwienny mózgu, udar lakunarny

INTRODUCTION

An increased concentration of total homocysteine is a still disputable as a independent risk factor for cardiovascular diseases and also a predictor of cerebrovascular diseases, especially of stroke (1). There is no doubt that hyperhomocysteinemia plays an im-

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portant role in the atherosclerotic and thromboembolic process and promotes them. The mechanisms of these processes are very complicated and depend on many factors like the concentration of foliate, vitamin B12 and B6. It is also important that the concentration of increased serum homocysteine correlates with the state of vascular damage. Experimental data suggest that homocysteine has an influence on the oxidative arterial injury, damaging the vascular matrix and augmenting the proliferation of vascular smooth muscle. Homocysteine also alters the coagulation properties of the blood and impairs endothelium-dependent vasomotor regulation.

The reference value of the normal homocysteine concentration is between 5-15 μmol/l and this value is widely and commonly used. In this paper we present and discuss the association between hyperhomocysteinemia and types of stroke according to the Oxfordshire Community Stroke Project (OCSP) (2).

MATERIAL AND METHODS

Patients

We examined 193 patients (tab. 1a, 1b, 2) with acute ischemic stroke (83 men and 110 women, aged 53 to 96 years, mean 71.60 years), successively admitted to the Department of Neurology and Epileptology of the Center for Postgraduate Medical Education in Warsaw. The diagnosis of ischemic stroke was based on a history of sudden onset of a fixed neurological focal deficit of presumed ischemic origin lasting more than 24 hours. CT of the brain was performed on all patients to exclude other causes of neurological symptoms. Patients were classified into one of four stroke types according to the OCSP classification: TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction) and POCI (Posterior circulation infarction) (2). Group characteristics (stroke patients and controls with other neurological disease) are summarised in table 3. The local Ethics Committee of the Center for Medical Postgraduate Education in Warsaw approved this study.

Table 1a. Demographic data of group: gender and age.

Gender		Group	
		Stroke patients	Controls
Female	N	110	19
	%	57.0%	55.9%
Male	N	83	15
	%	43.0%	44.1%

Chi-Square test = 0.02 P < 0.904

Table 1b. Demographic data of group: gender and age.

Age	N	Mean ± (SD)
Stroke patients	192	71.59 ± 10.96
Controls	34	71.15 ± 11.92

Two-tailed Student's t-test t = 0.22 P < 0.829

Table 2. The concentration of homocysteine in group patients with stroke and controls.

Concentration of homocysteine	N	Mean ± (SD)
Stroke patients	193	14.95 ± 6.19
Controls	34	13.06 ± 3.67

Manna Whitney U test z = -1.59 P < 0.113

Table 3. Demographic data of group HC1 (patients with homocysteine concentrations over 15 μmol/l) and HC2 (patients with homocysteine concentrations below 15 μmol/l).

Parameters		Total	HC1 > 15 μmol/l (n = 74)	HC2 < 15 μmol/l (n = 119)
Gender	Female	110	38 (51.4%)	72 (60.5%)
	Male	83	36 (48.6%)	47 (39.5%)
Age				
Mean		71.6	74.29*	69.89
± SD		± 10.9	8.76	11.84
95% CI		70.0-73.1	72.26-76.33	67.73-72.05
Median		73	75.5	72
75%		79	81	78
25%		67	68	63
min.		35	45	36
max.		95	91	95

Two-tailed Student's t-test HC1 vs HC2 *P < 0.0001

BLOOD SAMPLING AND QUANTIFICATION OF HOMOCYSTEINE CONCENTRATION

Peripheral blood was obtained in the first 48 hours after onset of symptoms of stroke. The blood has been immediately centrifuged. Serum was stored at -20°C. Total plasma homocysteine concentrations were measured by fluorescence polarisation immunoassay (FPIA-ABBOTT) (3). We considered a homocysteine concentration > 15 μmol/l as pathological basing our findings on Ueland's study (4). Therefore patients for analysis were divided into two groups: patients with the homocysteine concentration in sera < 15 μmol/l and the homocysteine concentration in sera > 15 μmol/l.

STATISTICAL ANALYSIS

The statistical analyses were performed by Statistica (StatSoft, USA) version 6.0. For descriptive purposes, univariate analysis with either the chi-square test or Fisher's exact test (depending on the sample size) was used to perform evaluation of frequency distribution proportionality for categorical variables, while one-way analysis of variance (ANOVA) was used for continuous variables. The statistical significance of differences between groups was evaluated by the non-parametric Mann-Whitney U test. Multivariate logistic regression with odds ratio (OR) was performed.

RESULTS

We found an increased pathological homocysteine concentration in 35.3% (74 cases – 38 female and 36 male) (tab. 3). We did not find statistical significance of differences between groups of stroke patients vs controls. It was evaluated by the non-parametric Mann-Whitney U test (tab. 2). Therefore we divided stroke pa-

tients group into two subgroups: patients with stroke and normal concentration of homocysteine and patients with stroke and with increased over 15 μmol/l (according to the FPIA-ABBOTT recommendation we take the concentration of homocysteine lower than 15 μmol/l as a normal). The presence of the highest concentrations was most frequently observed among patients with LACI (fig. 1). Compared to the total number group of examined stroke patients this concentration was significantly higher in the LACI group ($P < 0.007$) (fig. 3). Additionally, a homocysteine concentration > 15 μmol/l was observed in 41.9% of LACI patients. This was the highest statistically significant concentration ($P < 0.02$) compared to the other groups of patients (fig. 2). In the group of patients with PACI an increased homocysteine concentrations was found in 35.1% of subjects, while concentrations of 14.9% and 8.1% were found in TACI and POCI patients respectively (fig. 3).

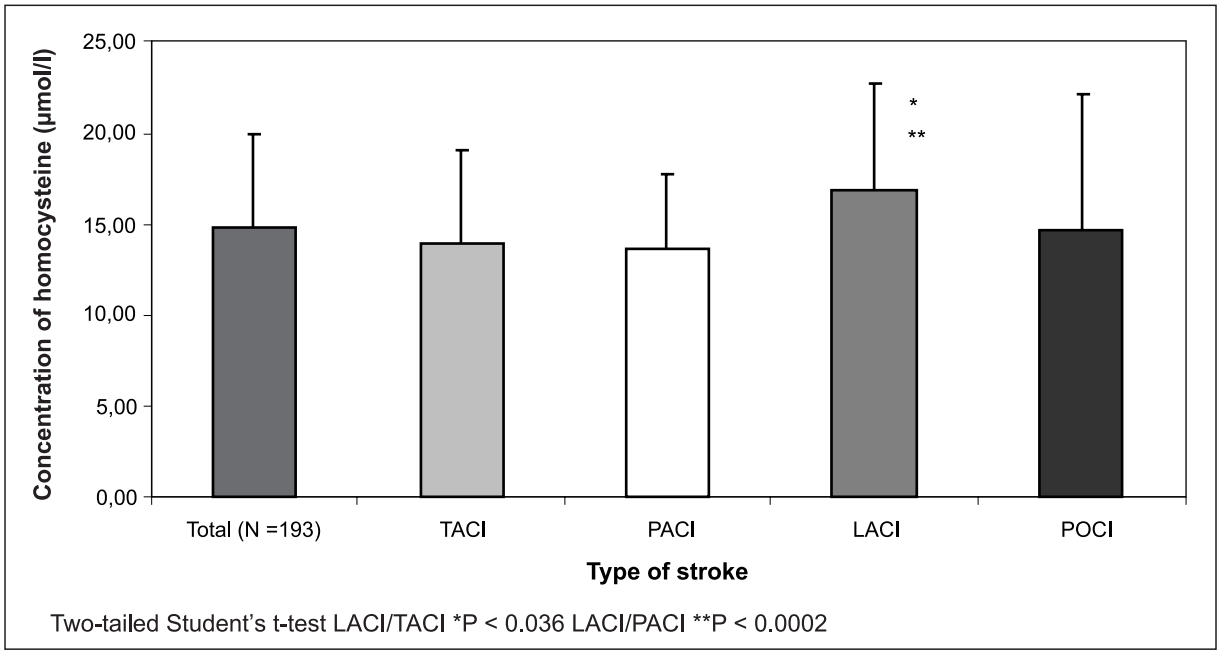

Fig. 1 Analysis of homocysteine concentrations vs. type of stroke according to the Oxfordshire Community Stroke Project (OCSP): TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction), POCI (Posterior circulation infarction).

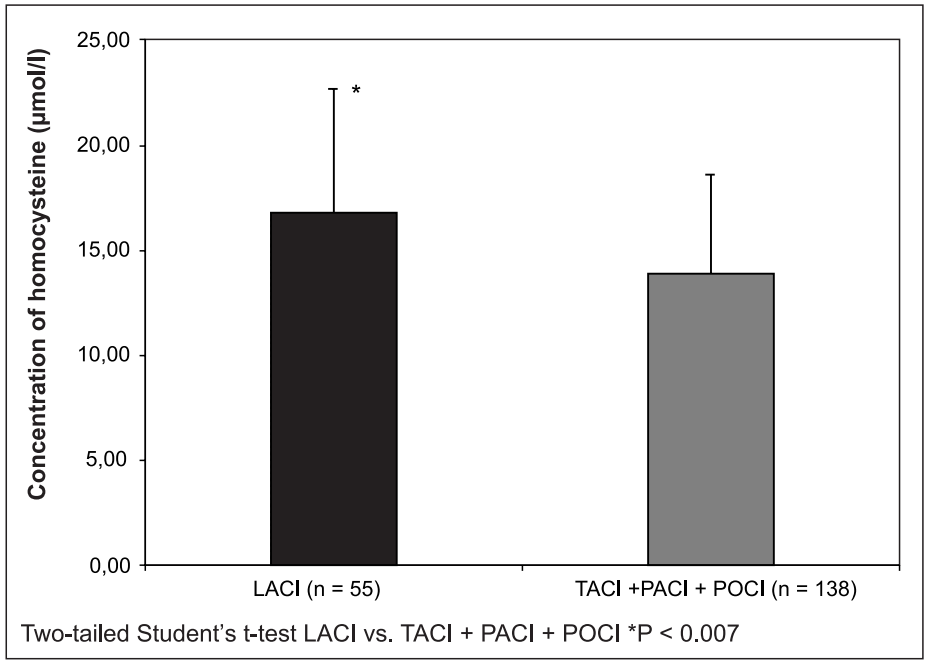

Fig. 2. Analysis of homocysteine concentrations – lacunar stroke vs. other types of stroke according to the Oxfordshire Community Stroke Project (OCSP): TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction), POCI (Posterior circulation infarction).

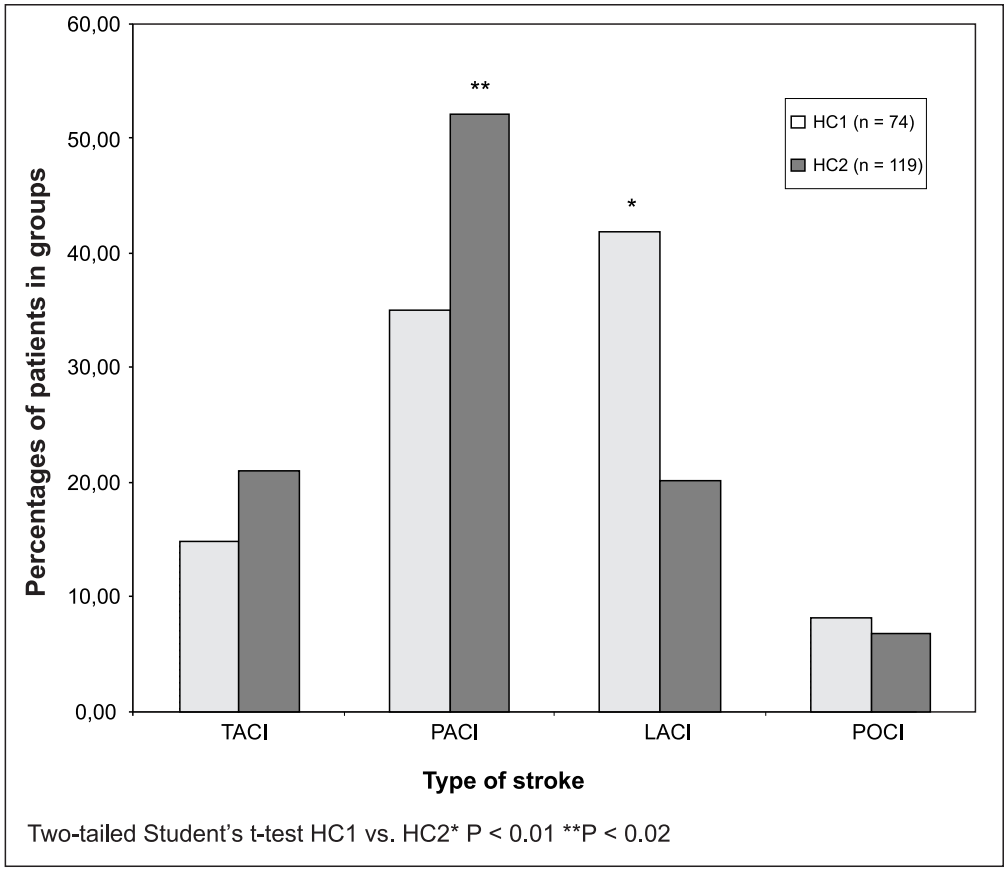

Fig. 3. Percentages of patients in groups vs. type of stroke according to the Oxfordshire Community Stroke Project (OCSP): TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction), POCI (Posterior circulation infarction) and homocysteine concentration – HC1 (patients with homocysteine concentration over 15 μmol/l) and HC2 (patients with homocysteine concentrations below 15 μmol/l).

Multivariate logistic regression analysis revealed that hyperhomocysteinemia was an independent and significant factor ($P < 0.0005$) with odds ratio (OR) of 1.11 (1.04 -1.19.95% confidence interval) for ischemic stroke and especially for LACI stroke compared to other types of stroke ($P < 0.0003$) with OR of 1.09 (0.98-1.16, 95% confidence interval) (tab. 4).

DISCUSSION

Elevated plasma homocysteine concentrations were first implicated in the pathogenesis of atherosclerosis about 30 years ago (5). The mechanisms underlying relationship to cardiovascular disease and explaining the toxic effects of homocysteine are unclear. Oxidation is one of the most favoured postulated mechanisms; others are nitrosylation, acylation, and hypomethylation (6). A moderately increased homocysteine concentration is an increased risk for ischemic stroke (7). Different epidemiological studies indicate that elevated plasma homocysteine is associated with an increased risk of atherothrombotic vascular events of the brain, heart and limbs and also show that this association is independent of other known risk factors. Additionally the data presented by Boysen et al. in their study (1) indicates that elevated total homocysteine is an independent risk factor for recurrent stroke.

Recent studies have shown that hyperhomocysteinemia also causes, endothelial dysfunction measured by impaired endothelium-dependent flow mediated vasodilatation in humans (7-12). This dysfunction appears to be age related and occurs mainly in older adults (13). The first epidemiological studies that identified an association between increased homocysteine concentration and ischemic stroke caused by large artery disease were also associated with carotid atherosclerosis. Results published in the last few years identified a significantly higher mean total homocysteine concentration in patients with ischemic stroke due to large and small artery disease and not cases of ischemic stroke due to cardiac embolism or other causes (7, 14, 15). In these studies it was observed that hyperhomocysteinemia might cause subcortical vascular encephalopathy due to cerebral microangiopathy. Mizrahi et al. (16) reported that a high plasma total homocysteine concentration is associated with a history of hypertension and recurrent stroke among patients presenting with acute ischemic stroke. Their results showed that hyperhomocysteinemia is independent of other risk factors such as atrial fibrillation, diabetes and hyperlipidemia. Hypertensive stroke patients with hyperhomocysteinemia should be identified as high-risk patients as compared to non-hypertensive stroke patients, and more vigorous measures for secondary

Table 4. Major risk factors for ischemic stroke in examined patients vs. types of stroke according to the Oxfordshire Community Stroke Project (OCSP): TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction), POCI (Posterior circulation infarction).

Parameters	Total	Types of stroke			
		TACI	PACI	LACI	POCI
Presence of risk factors yes/no (%)					
Atrial fibrillation	54/139 (28.0)	14/22 (38.90)	26/62 (29.5)	13/42 (23.6)	1/13 (7.1)
Hypertension	166/27 (86.0)	32/4 (88.9)	78/10 (88.6)	45/10 (81.8)	11/3 (78.6)
Diabetes	40/153 (20.7)	9/27 (25)	23/65 (26.1)	7/48 (12.7)	1/13 (7.1)
Infection before stroke	38/155 (19.7)	14/22 (38.9)	17/71 (19.3)	7/48 (12.7)	0/14 (0.0)
Hyperlipidemia	67/126 (34.7)	16/22 (44.4)	31/57 (35.2)	17/38 (30.9)	3/11 (21.4)
Smoking	46/147 (23.8)	8/28 (22.2)	19/69 (21.6)	14/41 (25.5)	5/9 (35.7)
Atherosclerotic changes in carotid arteries	76/117 (39.4)	20/16 (55.6)	32/56 (36.4)	22/33 (40)	2/12 (14.3)
Alcohol abuse	7/186 (3.6)	4/132 (11.1)	2/86 (2.3)	1/54 (1.8)	0/14 (0)
Previous stroke	38/155 (19.7)	8/28 (22.2)	21/67 (23.9)	8/47 (14.5)	1/13 (7.1)
Previous heart infarct	31/162 (16.1)	4/32 (11.1)	15/73 (17)	8/47 (14.5)	4/10 (28.6)
Coronary heart disease	175/18 (90.7)	36/0 (100)	76/12 (86.4)	50/5 (90.5)	13/1 (92.9)
Thrombotic events	10/183 (5.2)	5/31 (13.9)	3/85 (3.4)	1/54 (1.8)	1/13 (7.1)
Hyperhomocysteinemia	74/119 (38.3)	11/25 (30.6)	26/62 (26.5)	31/24 (56.7)	6/8 (42.7)

Multivariate logistic regression analysis revealed that hyperhomocysteinemia was an independent and significant factor ($P < 0.0005$) with odds ratio (OR) of 1.11 (1.04-1.19, 95% confidence interval) for ischemic stroke and especially for LACI stroke compared to other types of stroke ($P < 0.0003$) with OR of 1.09 (0.98-1.16, 95% confidence interval).

prevention may be warranted. Some authors suggest that increased concentration of hyperhomocysteine is strongly connected with arterial hypertension and may serve as a marker for the development of essential hypertension (17).

There is also presented that higher plasma homocysteine concentrations are associated with smaller brain volume and the presence of silent brain infarcts at MRI, even in healthy, middle-aged adults and it have not only vascular ethiopathology but also cellular mechanism play very important role. Thus, both cellular and vascular mechanisms may underlie the association of plasma homocysteine concentration with brain aging, as reflected by the effects on both subclinical and overt disease (15, 18).

In our study we found that hyperhomocysteinemia is an independent risk factor for ischemic stroke (tab. 4). Our results also determined the association of stroke events, especially lacunar stroke with a high homocysteine concentration (tab. 2). Results very similar to ours were presented by Abbate et al. (19).

The endothelial dysfunction caused by methionine-induced mild hyperhomocysteinemia affects conduit and resistance vessels (10, 11, 20). It is suggested that one important point of this process is reduction of the activity of the endothelium dependent relaxing factor nitric oxide and increased oxidant stress with alterations of the endothelial cellular redox potential. Published by Haltmayer et al. (21) results of the study demonstrate an association between total homocysteine and non-fatal atherothrombotic stroke in patients with symptomatic peripheral arterial disease.

In our group of stroke patients we observed a significant increase of homocysteine in the subgroup of patients with lacunar stroke. We think that the middle and small vessels are especially exposed to destruction and occlusion if the endothelial lining is significantly injured. Additionally, hyperhomocysteinemia stimulates the formation of clots if the smaller artery is not blocked off earlier. Such a process is observed in patients with coronary heart disease. Subjects with hyperhomocysteinemia are especially exposed to coronary heart disease. Blockages of coronary arteries due to atherosclerosis lead to coronary insufficiency and finally to infarct.

Japanese authors, the same like we, observed higher frequency of elevated homocysteine concentrations in groups of patients with lacunar stroke (22).

This type of stroke may cause impairment of cognitive functions and is associated with dementia. Other authors demonstrate the relation between the homocysteine concentration and age (23) or suggest that the risk of stroke is more serious in younger patients (< 60-65 years) (24, 25), especially in patients who show symptoms of vascular diseases (26). In our study we notice statistic differences of homocysteine concentration only among patients age between 40-50 ($p < 0.01$-0.03) and was lower than in other group. There were no statistically significant differences between homocysteine concentrations between all other age-range groups (two-tailed Student's t-test $p > 0.05$) (tab. 5).

There may be correlations between the concentration of increased serum homocysteine and the state of vascular damage. Hackam's uncontrolled study showed that it is possible to lower homocysteine by administering a combination of folic acid, vitamin B6 and vitamin B12, and in this way to reduce the progression of atherosclerosis measured by carotid plaque area. What concentration of plasma homocysteine should be treated? Hackam's study demonstrated the positive effects of vitamin therapy on the progression of

Table 5. Analysis of the homocysteine concentrations according to age of patients with stroke.

Age	n	% of whole group	Homocysteine concentration mean ± SD
40-50	10	1.3	9,94 ± 2,79[1,2,3,4]
51-60	16	8.4	14,24 ± 6.42
61-70	50	26.3	14.78 ± 4.70
71-80	78	41.0	15.03 ± 5.34
81-96	36	19.0	17.11 ± 9.06

Two-tailed Student's t-test.
[1]group age 40-50 vs age 51-60 $p < 0.03$
[2]group age 40-50 vs age 61-70 $p < 0.03$
[3]group age 40-50 vs age 71-80 $p < 0.02$
[4]group age 40-50 vs age 81-96 $p < 0.01$

carotid atherosclerosis in patients with homocysteine concentrations above and below 14 μmol/l (27, 28). Recently many authors have published report results which confirm this observation. By administering the above-mentioned vitamins the risk of recurrent cerebrovascular events can be prevented. It can thereby decrease the number of vascular complications of stroke and normalize elevated homocysteine concentrations (29-32). Unfortunately, no consensus on homocysteine management is available at present (33). There is a management trial to test whether a combination of folic acid, vitamin B6, and vitamin B12 did not reduce a combined end point of total cardiovascular events among high-risk women. After 7.3 years treatment and follow-up did not reduce a combined end point of total cardiovascular events among high-risk women, despite significant homocysteine lowering (34). In 2009 Tseng et al. (7) published their results that hyperhomocysteinemia is a risk factor for cerebral white matter lesion in stroke patients. Even mild hyperhomocysteinemia can significantly increase severity of cerebral microangiopathy. Oncel et al. (35) find that serum low-density lipoprotein, total cholesterol and homocysteine concentrations were associated with silent brain infarct. Knottnerus et al. (8) analyzed many papers where authors try to find mechanism of changes in arteries such as observed endothelial dysfunction which might be involved in the pathogenesis of lacunar stroke. They suggest that homocysteine is a toxin for the endothelium and it could be one of many factors which cause such changes. Dhamija et al. (36) found that raised homocysteine and serum lipoprotein concentrations were independently associated with ischemic stroke and with a significant positive correlation between the two parameters. Elevated homocysteine concentrations may modulate the toxicity of lipoprotein in ischemic stroke.

In our study the independence of these risk factors was not confounded by other factors associated with high homocysteine, such as the age of patients. There are opinions that traditional risk factors are especially useful in predicting future stroke than older ones (37). Therefore it is important to measure the concentration of increased serum homocysteine, which correlates with the state of vascular damage. Routine measurement of homocysteine concentrations may have a beneficial role in the prevention of stroke.

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